

## PASSIVE SMOKING AND LUNG CANCER

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**Summary** Questions about the smoking habits of parents and spouses were asked in a case-control study involving 1338 lung cancer patients and 1393 comparison subjects in Louisiana, USA. Non-smokers married to heavy smokers had an increased risk of lung cancer, and so did subjects whose mothers smoked. There was no association between lung cancer risk and paternal smoking. The association with maternal smoking was found only in smokers and persisted after controlling for variables indicative of active smoking. It is not clear whether the results reflect a biological effect associated with maternal smoking or the inability to control adequately for confounding factors related to active smoking. This preliminary finding deserves further investigation.

## Introduction

THE possibility of passive or involuntary smoking being a causative factor in lung cancer has been investigated in several countries.<sup>1-3</sup> This report describes a case-control study of lung cancer in Louisiana in which questions were asked about the smoking habits of the spouses and parents of 1338 lung cancer patients and 1393 comparison subjects (controls).

## Materials and Methods

Current primary lung cancer cases were identified from admission and pathology records of all participating hospitals in twenty-nine Louisiana parishes (counties), which included all southern, one central (Rapides), and two northern parishes (Caddo and Bossier). Patients with bronchioalveolar carcinomas (32 cases) are not included in the present report. All major hospitals in the study area participated except some in the city of New Orleans where, for logistic reasons, interviewing was deliberately limited to two large hospitals serving the medically uninsured population and two large private hospitals. For each subject a control was randomly selected from patients attending the same hospital and matched by race, sex, and age (within 5 years). Patients whose main diagnosis was emphysema, chronic bronchitis, chronic obstructive pulmonary disease, or cancer of the larynx, oral cavity, oesophagus, or bladder were excluded from the control selection procedures. The admission diagnoses of the controls were distributed in the following categories: cardiovascular 15.3%; gastrointestinal 13%; musculoskeletal 10%; genitourinary 7.3%; ophthalmology and otorhinolaryngology 6.6%; other tumours 5%; diabetes 5%; trauma 3.7%; peripheral vascular 3.7%; pulmonary 2.7%; cerebrovascular 2.5%; and infections 2%.

Local professional interviewers, trained for this investigation and thoroughly familiar with local culture, interviewed subjects (76% of the cases and 89% of the controls) or their next of kin. The questions covered occupation, residency, diet, smoking and drinking habits, health, water supply, and other related items. Information elicited on the smoking habits of the spouse or parent included type of material smoked, duration of smoking habit, and daily amount. Questions on parental habits referred to the period "during most of your childhood". Histological confirmation was obtained for 97% of the cases. Missing data were excluded from the tables. Standard unmatched pair methods were used to estimate relative risks. All *p* values are based on 2-sided  $\chi^2$  tests.

## Results

## Spouse Smoking

We identified non-smokers with lung cancer and compared the smoking histories of their spouses with those of spouses of non-smoking controls. Only 10 out of 1036 male cases were non-smokers: 2 reported occupational exposure to dust (street-sweeper, log-cutter); 1 was a steam-pipe fitter; 2 lived in the immediate vicinity of industrial plants (grain elevator and cement, oil refinery); 1 was married to a heavy smoker; and 4 were long-time chewers of tobacco. There were 25 non-smoking, ever-married women with lung cancer out of 302 female cases; 2 of these chewed tobacco regularly. For 1 female and 2 male non-smoking patients no information was available on the smoking history of the spouse. 2 female patients' husbands were smokers but the amount and duration was unknown.

Table 1 distributes the non-smoking, ever-married men and women according to total lifetime pack-years smoked by their spouses at the time of the interview. The relative risk of lung cancer is raised when the spouse is a heavy smoker.

Similar tabulations for smoking subjects did not show an increased risk associated with smoking of spouses, except for light smoking men (less than 20 pack-years), who had a relative risk of 1.5 when married to heavy smokers (41 pack-years or more). Case-control comparisons based on current daily number of cigarettes smoked by the spouse yielded almost identical findings, including relative risk estimates, with those presented in table 1. The apparent passive exposure effect was present in women over and under 60 years of age, although small numbers made the subgroup findings not statistically significant. Analyses limited to cases and controls interviewed in person indicated that systematic bias in personal versus next-of-kin responses can be ruled out as a potential explanation for the findings. The same conclusion was reached when relative risks were race adjusted. Inclusion of bronchioalveolar carcinomas resulted in slightly lower odds ratios: males 1.69; females 1.77, both sexes 1.75.

## Parents' Smoking Habits

Smoking habits of the parents strongly influenced smoking habits in offspring (table 1). Heavy smokers were more likely than the other patients to have had smoking parents. The smoking histories of the parents in our series were associated with each other. There were 201 spouse pairs of smokers, compared with 136 expected if the status of each parent was

TABLE 1—NON-SMOKING, EVER-MARRIED LUNG CANCER CASES AND CONTROLS AND LIFETIME CONSUMPTION OF CIGARETTES BY THEIR SPOUSES

	Cigarettes smoked by spouse (pack-years)		
	None	1-40	≥41
<b>Males</b>			
Cases	6	2	0
Controls	154	20	6
Odds ratio	1.0	2.0	
<b>Females</b>			
Cases	8	5	9
Controls	72	38	23
Odds ratio	1.0	1.18	3.52*
<b>Both sexes</b>			
Odds ratio (adjusted for sex)	1.0	1.48	3.11*

\**p* < 0.05

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TABLE II—CIGARETTE USE OF CONTROL SUBJECTS BY SMOKING CATEGORY OF THEIR PARENTS

	Father smoker		Mother smoker	
	Yes	No	Yes	No
<b>Males</b>				
Non-smokers	18%	32%	8%	27%
Ex-smokers	25%	26%	24%	26%
Current smokers	56%	42%	68%	47%
Total number	475	484	79	880
<b>Females</b>				
Non-smokers	37%	64%	29%	56%
Ex-smokers	20%	14%	15%	17%
Current smokers	43%	20%	56%	27%
Total number	130	154	34	250

independently distributed. Classification of the status of one member, particularly the mother, indirectly conveys information on the status of the marital partner.

When the smoking status of each parent is classified separately the relative risks of lung cancer for persons (both sexes, smokers and non-smokers) with a positive paternal and maternal history of smoking are 1.04 and 1.66, respectively (table III). Scrutiny of the data shows that the increased risk associated with maternal smoking is significant in smoking males (odds ratio 1.4) but not significant in smoking females (odds ratio 1.2). No significant increases in risk were found in non-smokers but small numbers preclude adequate analysis (there was only one non-smoking lung cancer patient whose mother was a smoker). To remove the confounding effect of the other parent, we considered each subset of cases and controls for which only one of the parents smoked. The respective relative risks, controlled for spouse-smoking status, for positive paternal and maternal histories of smoking were 0.95 and 1.47, respectively. Thus, smoking status of the mother increases the relative risk of lung cancer, but smoking status of the father does not. The effect of maternal smoking did not seem to be dose related; our questionnaire did not cover this point extensively because we doubted whether children could adequately quantitate their parents' smoking history. The relative risk of lung cancer when both parents smoked was 1.66; there is thus no evidence of an additional contribution to risk from paternal exposure, over and above that contributed by maternal exposure.

Given the enhancing effect of parental smoking on the smoking habits of the offspring, the effect of parental smoking on relative risk of lung cancer could reflect a subtle indirect association with active smoking by the subject. To control for active smoking, a logistic regression analysis was done, taking into account all the active smoking variables which increase lung cancer risk: age at which case started smoking, tar content of usual brand, degree of inhalation, use of hand-rolled cigarettes, years of smoking, maximum amount smoked. By this method of analysis the relative risk associated with maternal smoking was: 1.36 ( $p < 0.02$ ) for both sexes and 1.5 ( $p < 0.01$ ) for males. No increase in risk

TABLE III—LUNG CANCER CASES AND CONTROLS (BOTH SEXES COMBINED) ACCORDING TO PATERNAL AND MATERNAL SMOKING HISTORY

	Father smoker		Mother smoker	
	Yes	No	Yes	No
Lung cancer	579	590	182	1054
Control	615	652	126	1214
Odds ratio—crude	1.04		1.66†	
Odds ratio adjusted for active smoking (logistic regression—see text)	0.83		1.36*	

\* $p < 0.05$ . † $p < 0.01$ .

was found in this model for female subjects or for subjects whose fathers smoked. The risk was significantly raised only in male smokers whose mothers smoked.

### Discussion

#### Spouse-smoking Effect

Our data strengthen the contention that heavy smoking by one member of the spouse pair increases the lung cancer risk of the non-smoking partner. Heavy smoking by wives may increase the risk of the light smoking husband but this finding requires further analysis and confirmation in larger series. Smoking by husbands did not affect the risk of lung cancer in women who smoked (relative risk 1.03), a finding that suggests that active smoking is so powerful that it overshadows any possible additional effect from concomitant passive exposure.

The proportion of lung carcinomas that were adenocarcinomas in non-smoking women was 54%, compared with 22% for smoking women. The association of adenocarcinoma with smoking is weaker than for other histological types. The risk of squamous and small cell carcinomas among smokers, relative to a unit risk for non-smokers, has been reported to be 15.4, compared with 5.1 for adenocarcinoma.<sup>4</sup> Table I may therefore reflect dilution of the relation by inclusion of adenocarcinomas. Exclusion of adenocarcinomas produced a significant linear trend in risk, as found by Trichopoulos et al.<sup>2</sup> The possibility that differences in the chemical composition of mainstream (active) and sidestream (passive) smoke may produce different proportions of histological types of tumours should be considered. The nitrosamine content in sidestream smoke is reported to be approximately 50 times greater than that in mainstream smoke.<sup>5</sup>

The effect of the smoking habits of the spouse on lung cancer risk was first reported by Hirayama in a Japanese cohort study.<sup>1</sup> A cohort study in the United States reported a positive but not significant increase in risk for non-smoking women married to smoking husbands.<sup>3</sup> A case-control study of non-smoking women diagnosed as having lung cancer in Greece reported relative risks of approximately 2.5 for those married to moderate smokers and 3 for those married to heavy smokers, with a significant linear trend.<sup>2</sup> Our numbers are small but we think that the similarity between our findings and those of Trichopoulos et al.<sup>2</sup> strengthens the suspicion that passive smoking may contribute to lung cancer risk.

#### Parental Smoking Effect

As far as we know, ours is the first case-control study of lung cancer reporting on parental smoking history. Parents' smoking behaviour influences the smoking habits of their offspring,<sup>6,7</sup> but we found that the smoking behaviour of the father does not influence the lung cancer risk of his offspring, whereas the behaviour of the mother does. This difference may reflect the closer and more prolonged contact that infants and young children have with their mothers than with their fathers.

The risk of bronchitis and pneumonia is increased in children whose mothers smoke.<sup>8,9</sup> This effect is dose related and is greater in the winter, strongly suggesting that passive smoking by the infant is causally related to risk of respiratory infection. The excess of bronchitis occurs after 6 months of age, suggesting that the passive immunity transferred from mother to child prevents bacterial colonisation of bronchial mucosa. The effect of passive smoking on bronchitis may be independent of the mutagenic effect of the tobacco smoke,<sup>10</sup> and it is probably safe to assume that the child is exposed to

both the irritant and the mutagenic insults carried by sidestream smoke. The observation that the bronchitis attributable to passive smoking occurs mostly during the first year of life and is independent of birth weight may reflect the intimacy of mother-child contact in that period of the child's life.<sup>11</sup> Bronchitis in infants may have a long-lasting effect on the respiratory tract as suggested by the increase in the prevalence of cough at age 20 in subjects who have had a respiratory illness during the first 2 years of life, independent of current smoking habits.<sup>12</sup>

Whether bronchitis is a causative factor in lung cancer is confounded by the fact that smoking induces both cancer and bronchitis. Cohort studies have concluded that "persons who smoke cigarettes run a higher risk of chronic bronchitis than non-smokers and those who develop bronchitis run a higher risk of developing lung cancer".<sup>13</sup>

How maternal smoking causes lung cancer can at this stage only be a matter of speculation. By itself, passive smoking during childhood may not be sufficient stimulus for carcinogenesis. However, laboratory work has shown that transplacental exposure to carcinogens increases the carcinogenic response to post-natal exposure to the same or to a different carcinogen;<sup>14,15</sup> benzo(a)pyrene, a mutagenic carcinogen found in tobacco smoke, when injected into pregnant mice, induces cancer of the lung and other organs of the offspring;<sup>16</sup> tumours develop in 33% of the offspring of pregnant hamsters treated with high doses of cigarette smoke condensate;<sup>17</sup> and small doses of carcinogens can induce tumours in fetal tissue.<sup>18</sup>

The effects of maternal smoking are only significant in males, especially the heavy smokers. Perhaps maternal smoking enhances active smoking by the offspring in subtle ways not detected by conventional techniques. If our methods for controlling for active smoking are not sufficiently refined, the increase in risk associated with maternal smoking would not be an effect of passive smoking but one of enhancement of active smoking behavioural patterns. This is a real possibility and we would like to encourage further research on the subject.

#### Conclusion

The differences between the effects of passive exposure to spouse and maternal smoking are puzzling. Passive exposure to spouse smoking is mostly detected in non-smokers and light smoking males; maternal passive smoking effects are seen mostly in smokers. Passive smoking from spouses is introduced in adult life and in smokers is concurrent with their own active smoking. The magnitude of such an effect may be low when compared with active concomitant smoking and it may not be detectable when both types of smoking are present.

Maternal smoking, on the other hand, exerts its influences early in life and in the absence of active smoking is probably insufficient to produce carcinogenic effects. Our findings indicate that maternal smoking results in a slight increase in lung cancer risk but do not indicate whether the effect is due to enhanced active smoking of the offspring or to enhanced susceptibility to lung cancer induction after the challenge of active smoking later in life.

Our findings point to the need for more research on the subject of passive smoking and cancer. Since large numbers of cases may be needed for adequate epidemiological analysis, multi-institutional collaboration may be indicated.

This was supported by contract N01-CP-91023, DCCP, National Cancer Institute, National Institutes of Health (South Louisiana) and by a grant from the Louisiana Chapter of the American Cancer Society (North Louisiana).

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### ANAPHYLACTOID REACTIONS TO NEUROMUSCULAR BLOCKING AGENTS: A COMMONLY UNDIAGNOSED CONDITION?

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**Summary** A group of 28 patients with extreme, life-threatening sensitivity to suxamethonium was identified and 15 were studied in detail by skin-testing. The female/male ratio was 8/1. Sensitivity may be present without previous exposure to suxamethonium; in 3 patients reactions occurred during the first exposure to anaesthesia. Most patients showed one or more cross-sensitivities to alcuronium, tubocurarine, and gallamine. Signs of circulatory collapse were the sole presenting feature in 50% of the patients. Histamine release induced by the drug in vitro was demonstrated in some instances.

#### Introduction

DRUGS of the muscle-relaxant group are commonly implicated in systemic reactions, sometimes life-threatening, which occur during general anaesthesia. Since 1977 patients at our hospital who have had severe anaesthetic reactions have been skin-tested to determine drug sensitivity. After two deaths attributed to suxamethonium in Auckland in 1982, a study of known sensitive patients was undertaken, initially to determine whether 'Ethycholine', the only suxamethonium chloride available in New Zealand, differed in provoking

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